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Total Number of Pages in This Submission: **8**

Application Number	**09/716,842**
Filing Date	**November 17, 2000**
First Named Inventor	**BRIESEWITZ, ROGER**
Group Art Unit	**1644**
Examiner Name	**HUYNH, PHUONG NEON**
Attorney Docket Number	**STAN-131**

ENCLOSURES (check all that apply)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
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- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
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- ☐ Assignment Papers *(for an Application)*
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- ☐ Licensing-related Papers
- ☐ Petition
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- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)* ***Appellants' Reply Brief (7 pgs.)***
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below):*

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature	
Date	**November 7, 2006**

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APPELLANTS' REPLY BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/716842
	Confirmation Number	8224
	Attorney Docket No.	STAN-131
	Filing Date	November 17, 2000
	First Named Inventor	BRIESWITZ, ROGER
	Examiner	HUYNH, PHUONG NEON
	Group Art	1644
	Title: *TARGETED BIFUNCTIONAL MOLECULES AND THERAPIES BASED THEREON*	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on September 13, 2006

Please charge any required fees to deposit account number 50-0815, order no. STAN-131.

In this Reply Brief, the Appellants address comments made in the Examiner's Answer mailed September 13, 2006. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated in full herein solely in the interest of brevity and for the convenience of the Board.

Withdrawn Rejection

Appellants express gratitude in the Examiner's indication that the rejection of Claims 16-18, 22-26, 30-34, and 36 under 35 U.S.C. §112, first paragraph, has been withdrawn.

Response to Arguments

I. Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are not obvious under 35 U.S.C. §103(a) over Forsgren et al (Cancer Res. 39(12):5155-64 (1979)) in view of WO 95/02684.

In the Examiner's Answer, the Examiner maintains the rejection of Claims 16-18, 22-23, 30-34, 36, and 39-56 under 35 U.S.C. §103(a) as allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)), in view of WO 95/02684.

Scope of Claims

The Examiner asserts that "the scope of the independent claims 16, 24, and 30 merely require any peptidyl-prolyl isomerase ligand that [is] linked to a drug as a bifunctional molecule having a molecule weight that does not exceed about 5000 Daltons for a method of directing the distribution of said drug to any intracellular space. The claims do not recite the particular peptidyl-prolyl isomerase 'ligand' as the targeting moiety in the bifunctional molecule as long as it binds to intracellular biodistributed protein" (Examiner's Answer, page 8).

The Appellants respectfully disagree. As shown below, Claims 16, 24, and 30 all recite that the targeting moiety of the bifunctional compound is a peptidyl-prolyl isomerase ligand:

Claim 16:
"a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety comprising said drug or an active derivative thereof and **a targeting moiety to an intracellular biodistribution modulating protein** optionally joined by a linking group, **wherein** said drug moiety binds to a protein target and **said targeting moiety is a peptidyl-prolyl isomerase ligand**"

Claim 24:
"a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and a targeting moiety optionally joined by a linking group, **wherein said** drug moiety and **targeting moiety bind to intracellular proteins and said targeting moiety is a peptidyl-prolyl isomerase ligand**,

Claim 30:
"a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons and consisting of said drug moiety comprising said drug or a derivative thereof covalently linked, either directly or through an optional linking group, to **a targeting moiety that binds to an intracellular biodistribution modulating protein**, **wherein** said drug moiety binds to an intracellular protein and **said targeting moiety is a peptidyl-prolyl isomerase ligand**."

Remarks

The Appellants maintain that the Examiner's *prima facie* case of obviousness is deficient because the cited references fail to provide the requisite suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. The Examiner's *prima facie* case of obviousness is deficient for at least the following reasons:

1. the cited references do not teach modulation of biodistribution in the context of a peptidyl-prolyl isomerase ligand or the corresponding receptor; and
2. the cited dereferences do not teach use of a peptidyl-prolyl isomerase ligand as a targeting molecule.

The Examiner continues to assert that "it would have been obvious to one of ordinary skill in the art at the time the invention maws made to substitute the estrogen targeting moiety that [is] linked to a drug as taught by Forsgren et al for any one of the binding pair as a targeting moiety such as peptidyl-prolyl isomerase ligand, i.e. FK506, rapamycin or derivative thereof that bind to intracellular distributed receptor FKBP or cyclosporine...as taught by the WO 95/02684 publication for a method for directing the biodistribution of a drug as taught by Forsgren et al to the intracellular distributed receptor as taught by WO 95/02684 publication" (Examiner's Answer, page 5).

However, the Examiner's argument with respect to motivation to combine the references is deficient in that it is premised on using the teaching of targeting and modulation of biodistribution with respect to 17β-Estradiol from Forsgren et al. and applies this teaching to a completely different compound, namely an FKBP receptor or a peptidyl-prolyl isomerase ligand.

As noted in greater detail in the Appeal Brief filed on June, 23, 2006, WO 95/02684 teaches a system that includes two elements: (1) chimeric proteins and (2) ligand molecules capable of oligomerizing the chimeric proteins. According to the cited reference, the chimeric protein includes a ligand-binding (or "receptor") domain fused to an action domain capable of initiating apoptosis (see page 3, lines 24-26). The cited reference further teaches that the receptor domain of such chimeric proteins are "capable of **binding to** FK-506-type ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand" that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasis added).

The cited reference does not teach: (1) that either the receptor or the peptidyl-prolyl isomerase ligand can be used in conjunction with a drug moiety in order to achieve a modulation of biodistribution of the drug moiety, and (2) that a peptidyl-prolyl isomerase ligand can be used as a targeting domain of a chimeric molecule. The Examiner incorrectly relies on a similar teaching with respect to 17β-

Estradiol in Forsgren et al., and applies this teaching to the receptor or the peptidyl-prolyl isomerase ligand of WO 95/02684.

According to Examiner's position, either the receptor or the peptidyl-prolyl isomerase ligand of WO 95/02684 can be substituted for the 17β-Estradiol domain of Forsgren et al. However, **there is no teaching or suggestion in either reference that the receptor or the peptidyl-prolyl isomerase ligand of WO 95/02684 would impart that same targeting and modulation of biodistribution properties as those described for the 17β-Estradiol targeting domain.** Therefore, there is no suggestion or motivation to modify or combine the teaching of the cited references. As such, the Examiner's *prima facia* case of obviousness is deficient.

The Federal Circuit has held that the motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. In *In re Napier*, the Federal Circuit held that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination".[1]

With respect to the present rejection, the deficiency is not simply that there is no express suggestion to modify or combine the references. Instead, the cited references simply do not teach that either the receptor or the peptidyl-prolyl isomerase ligand can be used in conjunction with a drug moiety in order to achieve a modulation of biodistribution of the drug moiety. Without such a teaching, even an implicit suggestion would be insufficient for a person having skill in the art to appreciate that the receptor or peptidyl-prolyl isomerase ligand of WO 95/02684 can be substituted for the 17β-Estradiol domain of Forsgren et al. and achieve similar biodistribution and targeting results. This teaching is only present in the present application.

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1 I*n re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995) (*see also Alza Corp. v. Mylan Laboratories Inc.*, 391 F.3d 1365 (Fed. Cir. 2004).

Moreover, the Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not the applicant's specification. In *In re Lee*, the Federal Circuit notes that it is improper "[use] that which the inventor taught against its teacher" in determining whether a person of ordinary skill would have been led to this combination of references.[2]

As noted above, the teaching of using the FKBP receptor or the peptidyl-prolyl isomerase ligand as a targeting domain in order to provide for a modulated biodistribution only appears in the present application. Therefore, it would be unreasonable to assume that the receptor molecule, much less the ligand molecule, can be substituted with the 17β-Estradiol domain of the bifunctional molecule of Forsgren et al., and result in a modulated biodistribution of the bifunctional molecule in a host. The only teaching to this effect is found in the Appellant's patent application.

Accordingly, since the *prima facia* case of obviousness has not been met the combination of the cited references cannot render the present application obvious. As such, the Appellants respectfully request that this rejection be withdrawn.

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2 *In re Lee*, 277 F.3d 1338, 1343, *citing W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 313-313 (Fed. Cir. 1983).

SUMMARY

The Appellant respectfully requests that the rejections of Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 under 35 U.S.C. §103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: NOV. 7, 2006

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